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DIALYSIS – TRANSPLANTATION

Recurrent ANCA-associated small vessel vasculitis after transplantation: A pooled analysis

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Recurrent ANCA-associated small vessel vasculitis after transplantation: A pooled analysis.

Background. Recurrent antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (ANCA-SVV) after renal transplantation has been described in case series. However, general information regarding the frequency, character, and predictors of recurrent disease after transplantation is currently lacking. We considered the rate of relapse, whether a positive ANCA at the time of transplantation predicted relapse, and whether cyclosporine A prevented recurrent disease.

Methods. We performed a pooled analysis of published data, added to the experience at the Universities of North Carolina (14 patients) and Lund, Sweden (11 patients). To avoid reporting bias, only case series were included for analysis. Subgroup analysis was performed by disease category (Wegener's granulomatosis, microscopic polyangiitis, or necrotizing crescentic glomerulonephritis) and ANCA staining pattern.

Results. ANCA-SVV recurred in 17.3% of all patients (N = 127), in 20% of cyclosporine A-treated patients (N = 85), and in 25.6% of patients with circulating ANCA at the time of transplantation (N = 39). There was no statistically significant difference in the relapse rate between patients treated and those not treated with cyclosporine A (P = 0.45), between those with and without circulating ANCA at the time of transplant (P = 0.75), or between patients with Wegener's granulomatosis and those with microscopic polyangiitis or necrotizing crescentic glomerulonephritis alone (P = 0.62).

Conclusion. There is a substantial relapse rate in the ANCA-SVV population. Therapy with cyclosporine A does not protect against recurrent ANCA-SVV, and the presence of a positive ANCA at the time of transplantation does not preclude transplantation. These conclusions must be substantiated with a prospective study of renal transplantation in patients with ANCA-SVV so as to optimize their management.

Despite better recognition and improved treatment of anti-neutrophil cytoplasmic antibody ANCA-associated small vessel vasculitis (ANCA-SVV) and glomerulonephritis, this group of diseases continues to cause end-stage renal disease in a substantial proportion of patients. As a result, one would anticipate that the number of patients with ANCA-SVV and end-stage renal disease will increase, bringing to the forefront issues pertaining to renal transplantation in this patient population.

Successful renal transplantation in patients with ANCA-SVV has been reported in multiple case reports [1–3]. These include patients who were in full remission and with negative ANCA tests, but also patients in remission with positive ANCA tests at the time of transplantation [abstract; Noel, *Clin Exp Immunol* 93(Suppl 1):43, 1993] [4–7] and even in patients with evidence of active vasculitis at the time of transplantation [8].

Recurrent disease after transplantation has also been described in several case reports. These recurrences have occurred as early as a few days post-transplantation [9, 10] and as late as several years post-transplantation [11–16]. Just as with the initial ANCA-SVV, reported recurrences after transplantation cover a spectrum of various organ involvement in addition to the transplanted kidney [12, 14, 17].

Although these case reports give an idea of the possible outcomes of renal transplantation in patients with ANCA-SVV, they fail to provide general information regarding the frequency and timing of recurrent disease, the effect and importance of clinical remission and of circulating ANCA prior to transplantation on outcome and risk of recurrent disease, and the effect of antirejection therapy in general and of cyclosporine A in particular in preventing relapses [18].

To date, several case series have reported recurrence rates ranging from 11 to 50%. These series are, however, too small to provide statistically meaningful data. Because the number of patients with ANCA-SVV who undergo renal transplantation is small in any center, such questions are unlikely to be answered by any individual group. For this reason, we performed a pooled analysis

Key words: relapse, ANCA, renal transplantation, cyclosporine A, end-stage renal failure.

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of the published data regarding renal transplantation in patients with ANCA-SVV, adding to it reviews of the experiences at the University of North Carolina and the Glomerular Disease Collaborative Network (GDCN) and the experience at the University of Lund, Sweden.

The aim of this study is to assess the outcome of renal transplantation in patients with ANCA-SVV, the rate of relapse of ANCA-SVV post-transplantation, the effect of a positive ANCA on the rate of relapses, and the effect of cyclosporine A on the rate of relapse.

METHODS

A computerized literature search was performed using MEDLINE and the following terms: transplantation, vasculitis, ANCA, Wegener's granulomatosis, and microscopic polyangiitis. All reports in the English language were reviewed, including a review of the cited references. In order to avoid reporting bias, only case series (including more than one patient) were included for the pooled analysis. In reviewing these case series, patients in whom the diagnosis of ANCA-SVV was established retrospectively were retained in the pooled analysis only when ANCA-SVV could be documented to be the cause of renal failure based on the clinical presentation (for example, rapidly progressive glomerulonephritis, SVV, hematuria, and proteinuria). (For this reason, one patient whose renal failure was attributable to chronic infection was excluded from analysis in the report by Stegeman et al [6]). Because of prior literature reviews, care was taken to count reported patients only once.

Data derived from the University of Lund (11 patients), and the University of North Carolina and GDCN (14 patients) were added to the data derived from the literature review. The GDCN is a group of 250 nephrologists from 80 private community offices and three medical schools, primarily located in North Carolina and the southeast region of the United States. The pooled analysis was performed by looking at the overall rate of recurrence of ANCA-SVV, as well as the recurrence rates for patients with a positive ANCA and those treated with cyclosporine A. A subgroup analysis was also performed based on disease category (Wegener's granulomatosis vs. microscopic polyangiitis or necrotizing crescentic glomerulonephritis) and the ANCA staining pattern or antigen specificity. The specific disease category for each individual patient was as determined by the authors of each report, regardless of the year of publication and the criteria used to establish that diagnosis. As ANCA testing has evolved and become more widely accessible over the years, the reports of these tests are not uniform among the various published reports. In an effort towards unification, C-ANCA and anti-PR3 ANCA were grouped together, and so were P-ANCA and anti-MPO ANCA.

To evaluate the effects of circulating ANCA, treatment with cyclosporine A, disease category, and ANCA pattern on disease recurrence, continuity adjusted chi-square and Fisher's exact tests were performed. A Wilcoxon rank-sum test was used to compare the time on dialysis (continuous variable) between patients who relapsed and those who did not. As data for ANCA testing or immunosuppressive regimen were not always available, only patients for whom such data were described were included in the analysis of each variable.

Definition of relapse

A patient was considered to have a relapse if at least one of the following criteria occurred [19, 20]: (*a*) a rapid rise in serum creatinine accompanied by an active urine sediment; (*b*) a renal biopsy demonstrating active necrosis or crescent formation; (*c*) hemoptysis, pulmonary hemorrhage, or new or expanding nodules without evidence for infection; (*d*) active vasculitis of the respiratory or gastrointestinal tracts as demonstrated by endoscopy with biopsy; (*e*) iritis or uveitis; (*f*) new mononeuritis multiplex; or (*g*) necrotizing vasculitis identified by a biopsy in any tissue. The documentation of a rise in ANCA titer was not necessary for the establishment of a relapse. For the pooled analysis, the rate of relapse for each study was based on the respective authors' assessment, as detailed clinical data were not always available for each reported patient.

RESULTS

Experience of the University of North Carolina and the Glomerular Disease Collaborative Network

Fourteen patients (five females and nine males) followed within the GDCN received a total of 15 transplants. Six patients had microscopic polyangiitis. Five patients had necrotizing and crescentic glomerulonephritis alone, and three had Wegener's granulomatosis. Eight patients had P-ANCA, and five had C-ANCA. The mean duration on dialysis prior to transplantation was 16 months (range 0 to 48 months). Nine patients received grafts from cadaveric donors, and six received grafts from living-related donors. The mean age at transplantation was 42 years. The mean time of follow-up post-transplantation was 44 months (3.6 to 110 months).

One of 15 transplants was lost due to early thrombosis. For the remaining 14 grafts, 11 patients were treated with cyclosporine A. At the time of the last visit, nine patients had a functioning graft, with an average serum creatinine of 2.0 mg/dl (1.3 to 2.2 mg/dl). No patient had any evidence of recurrent ANCA-SVV or glomerulonephritis. Four patients lost their grafts because of acute ($N = 1$) or chronic rejection ($N = 3$), and one patient suffered from early thrombosis.

Experience at the University of Lund

Eleven patients (2 females and 9 males) received a total of 13 transplants (one patient received 3 grafts). Seven patients had microscopic polyangiitis and four patients had Wegener's granulomatosis. The four patients with Wegener's granulomatosis and two patients with microscopic polyangiitis had anti-PR3 antibodies; all the other patients had anti-MPO antibodies. Two grafts were from living-related donors, and the remaining 11 were from cadaveric donors. All patients received cyclosporine A. The mean age at transplantation was 52.4 years (range 29 to 73 years). The mean time of follow up post-transplantation was 71 months (range 2 to 129 months).

Two patients with microscopic polyangiitis suffered recurrent disease at 26 and 36 months post-transplantation, respectively. In one patient, the relapse was associated with a loss of graft function.

By December 1997, four patients had died 2, 69, 97, and 122 months post-transplantation. One patient died two months post-transplant secondary to severe pneumonia and pneumothorax. Six patients had functioning grafts with a mean creatinine of 1.7 mg/dl (1 to 2.9 mg/dl).

Pooled analysis

Twenty-five reports of kidney transplants published between the years 1970 and 1997 were identified. Of these, only nine were case series, including more than one patient, and were included in the pooled analysis [4–6, 8, 21–25]. The two patients reported by van Ypersele de Strihou et al [26] were also included in the review by Kuross, Davin, and Kjellstrand [21]. For this reason, this article was not included separately in the pooled analysis. Nine of the 15 patients with Wegener's granulomatosis recently reported by Haubitz et al [24] were previously included in the report by Schmitt et al [8]. For this reason, only the remaining 11 patients in Schmitt et al's report were included in the pooled analysis. A total of 127 patients was available for analysis of relapse. Of the 25 patients with crescentic glomerulonephritis in the review by Nyberg, only two patients had documented positive ANCA tests [23]. Little information was given about the 23 other patients with crescentic glomerulonephritis. These were therefore not included in the pooled analysis because of the inability to ascertain from the article that these patients had ANCA-associated pauci-immune necrotizing glomerulonephritis. Data regarding ANCA titers at the time of transplantation were available on 59 patients, and data regarding immunosuppressive treatment were available on 86 patients. Because identification of patients with relapsing disease was not always complete, the analysis of relapse rate among patients with circulating ANCA at transplantation could be conducted on only 39 patients.

Recurrent ANCA-SVV disease occurred in 22 of 127 patients, corresponding to a relapse rate of 17.3% (Table 1). The average time to relapse was 30.9 months, ranging from 4 to 89 months. Of the 21 patients with recurrent disease for whom clinical information was available, renal involvement occurred in 12 patients, whereas 10 patients had relapsing disease affecting extra-renal organs only. Recurrent vasculitis affecting the upper respiratory tract occurred in eight patients, the lungs in six patients, the gut in two, the skin in four, the joints in four, and the eyes in two.

Table 1. Recurrent antineutrophil cytoplasmic antibody-associated small vessel vasculitis (ANCA-SVV) in all reported patients

Study	[Ref]	Patients *N*	Relapse *N*	Relapse %
Kuross	[21]	9	1	11.1
Schmitt	[8]	11	3	27.3
Haubitz	[13]	18	4	22.2
Stegeman	[6]	8	2	25
Grotz	[22]	4	2	50.0
Rostaing	[5]	8	1	12.5
Frasca	[4]	3	0	0.0
Nyberg	[23]	19	5	26.3
Allen	[25]	22	2	9.1
UNC		14	0	0.0
Lund		11	2	18.2
Total		127	22	17.3

The length of renal replacement therapy prior to transplantation was available on 7 patients who suffered a relapse and 41 patients who did not relapse. The seven patients with recurrent disease were on dialysis for 7, 18, 18, 21, 38, 144, and 182 months (median = 21 months). The median time on dialysis among patients who did not have a relapse was 17 months (range 0 to 63 months). There was no statistically significant difference in the distribution of time on dialysis prior to transplantation between relapsers and nonrelapsers.

Of the 16 patients with relapse for whom treatment information was available, 12 received cyclophosphamide, 3 received azathioprine (in addition to cyclosporine A and prednisone), and 1 received high-dose methylprednisolone alone. The treatment of recurrent disease afforded long-term remission or remission of therapy in 11 patients. Two relapses were associated with graft loss, and one patient was described as having a "remission of extra-renal vasculitis" but continued to have deteriorating renal function [24]. One patient died as a consequence of relapse.

Among patients treated with cyclosporine A ($N = 85$), recurrent disease occurred in 17 patients, corresponding to a relapse rate of 20% (Table 2). There was no statistically significant difference in the relapse rate between patients treated with cyclosporine A and those not receiving cyclosporine A ($P = 0.45$). Among patients known to have circulating ANCA at the time of transplantation

Table 2. Recurrent (ANCA-SVV) among cyclosporine A treated patients

Study	[Ref]	Patients *N*	Relapse *N*	Relapse %
Kuross	[21]	NA		
Schmitt	[8]	11	3	27.3
Haubitz	[13]	18	4	22.2
Stegeman	[6]	NA		
Grotz	[22]	4	2	50.0
Rostaing	[5]	8	1	12.5
Frasca	[4]	3	0	0
Nyberg	[23]	19	5	26.3
Allen	[25]	NA		
UNC		11	0	
Lund		11	2	18.2
Total		85	17	20.0

NA, data are not available or incomplete.

Table 3. Recurrent (ANCA-SVV) among patients with positive ANCA at transplantation

Study	[Ref]	Patients *N*	Relapse *N*	Relapse %
Kuross	[21]	NA		
Schmitt	[8]	NA		
Haubitz	[13]	6	2	33.3
Stegeman	[6]	6	2	33.3
Grotz	[22]	4	2	50.0
Rostaing	[5]	8	1	12.5
Frasca	[4]	3	0	0
Nyberg	[23]	12	3	41.7
Allen	[25]	NA		
UNC		NA		
Lund		NA		
Total		39	10	25.6

NA, data are not available or incomplete.

($N = 39$), recurrent disease occurred in 10 patients, corresponding to a relapse rate of 25.6% (Table 3). There was no statistically significant difference in relapse rate between patients with circulating ANCA and those without circulating ANCA at the time of transplant ($P = 0.75$).

The analysis of relapse by disease category revealed a rate of relapse of 20.4% among patients with Wegener's granulomatosis alone compared with 15.7% for patients with microscopic polyangiitis or necrotizing crescentic glomerulonephritis (Table 4). There was no statistically significant difference in the rate of relapse between the two disease categories ($P = 0.62$). Similarly, patients with C-ANCA were no more likely to suffer a relapse than patients with P-ANCA (20 vs. 17.2%, respectively, $P = 0.99$).

DISCUSSION

Despite the better recognition and improved treatment of ANCA-SVV and glomerulonephritis, this group of diseases continues to cause end-stage renal disease in a substantial proportion of patients. End-stage renal disease in the setting of ANCA-SVV can be the result of an acute rapidly progressive glomerulonephritis causing severe irreversible glomerular damage or of chronic scarring and slow progression to end-stage renal disease after a period of remission with therapy. In the setting of acute renal failure caused by ANCA-associated rapidly progressive glomerulonephritis, the renal outcome of patients is in a large part determined by the rapidity with which a diagnosis is established and immunosuppressive therapy is commenced. As such, the serum creatinine level at the time treatment is started is the single most important predictor of renal outcome [27]. In addition, in our experience, the majority of "treatment resistance" can be attributed to a delay in the initiation of immunosuppressive therapy [19]. Despite early institution of appropriate treatment, treatment resistance still occurs in approximately 3% of patients [19]. However, the majority of end-stage renal disease is the result of either repeated inflammatory insult to the kidneys or slowly progressive fibrosis and glomerulosclerosis after an acute flare of necrotizing glomerulonephritis. Because of these phenomena, approximately 20% of patients eventually reach end-stage renal disease and the need for renal replacement therapy over a period of mean follow-up of 32 months [19, 20, 25].

Renal transplantation has been recognized as an option of renal replacement therapy, and reports of successful transplantation in patients with ANCA-associated Wegener's granulomatosis, microscopic polyangiitis, or necrotizing crescentic glomerulonephritis date back to 1972. Because the majority of these reports are limited to individual cases or small case series, we pooled data from published data and our own experience in order to address better the important issues related to the long-term outcome of patients with ANCA-SVV after transplantation.

Our results show that the overall risk of recurrent ANCA-SVV is 17%, with an average time from transplantation to relapse of 31 months. This rate is somewhat lower than the expected rate reported in nontransplant patients, which ranges from 30 to 45% [19, 20, 28]. It is difficult, however, to compare these average rates of relapse because the time to relapse is measured differently in each case. In the study of relapse after transplantation, the time to relapse is measured from the time of transplantation, whereas in the nontransplant patient cohorts, the time to relapse is measured from either the end of treatment (in our study) or an arbitrary time after the initiation of treatment or from the beginning of treatment. Keeping this caveat in mind, this apparent decrease in the rate of relapse probably is attributable to the chronic immunosuppressive regimen required to prevent rejection post-transplantation.

The presence of ANCA at transplantation does not

Table 4. Recurrence of ANCA-SVV: Subgroup analysis by disease category and ANCA pattern

Study	[Ref]	Total patients	WG	WG relapse	MPA/GN	MPA/GN relapse	C ANCA	C ANCA relapse	P ANCA	P ANCA relapse
			N							
Kuross	[21]	9	9	1	0	0	NA	NA	NA	NA
Schmitt	[8]	11	11	3	0	0	11	3	0	0
Haubitz	[13]	18	15	3	3	1	13	3	3	1
Stegeman	[6]	8	2	1	6	1	3	1	5	1
Grotz	[22]	4	3	2	1	0	3	2	1	0
Rostaing	[5]	8	3	0	5	1	4	0	4	1
Frasca	[4]	3	0	0	3	0	0	0	3	0
Nyberg	[23]	19	4	1	15	3	NA	NA	NA	NA
Allen	[25]	22	NA	NA	NA	NA	NA	NA	NA	NA
UNC/GDCN		14	3	0	11	0	5	0	8	0
Lund		11	4	0	7	2	6	0	5	2
Sum		127	54	11	51	8	45	9	29	5
%				20.4		15.7		20.0		17.2

Abbreviations are: WG, Wegener's granulomatosus; MPA/GN, microscopic polyangiitis or necrotizing crescentic glomerulonephritis alone; NA, data not available or incomplete.

appear to increase the rate of relapse post-transplantation. The data from the pooled analysis are limited not only by the small number of patients for whom data exist, but also by the various techniques in ANCA testing over the years and center to center differences. This is probably more true for the antigen-specific tests for PR3 than MPO, as these tests have become widely available only recently, and there continues to be a significant variation in the results from one testing kit to the other.

Therapy with cyclosporine A does not appear to have a significant protective effect on recurrent ANCA-SVV over that afforded by other immunosuppressant regimens (corticosteroids and azathioprine). Assessing the effect of cyclosporine A depends on comparing patients treated with cyclosporine A with those not receiving the drug. With the advent of cyclosporine A in the mid-1980s, the number of patients not receiving cyclosporine A became very small, and any comparison introduces the additional chronological bias. Such a bias, however, theoretically should not affect the incidence of relapsing ANCA-SVV. Whether or not cyclosporine A affords some degree of protection from relapse in nontransplant patients or whether it has a role in the primary treatment of ANCA-SVV without a concomitant use of corticosteroids or azathioprine cannot be determined from this study. The last two years have seen the introduction of mycophenolate mofetil to the antirejection armamentarium. Evaluation of the role of mycophenolate mofetil in the treatment of ANCA-vasculitis is in its infancy, and it remains to be seen if this drug will reduce the incidence of recurrent disease post-transplantation.

Our pooled analysis revealed no difference in the rate of relapse post-transplantation among patients with Wegener's granulomatosis as compared with those with microscopic polyangiitis or necrotizing crescentic glomerulonephritis alone nor was there a difference based on ANCA pattern (C-ANCA or P-ANCA) or antigen specificity (PR3 or MPO). These results are somewhat different from our patient population with primary ANCA-SVV. In our cohort of 142 patients treated with corticosteroids and cyclophosphamide and followed over a mean of 26 months, we found that a diagnosis of Wegener's granulomatosis is associated with an increased trend for relapse as compared with patients with microscopic polyangiitis or glomerulonephritis alone (42% relapse vs. 30 and 20%, respectively). These different rates of relapse were not statistically different ($P = 0.63$). Conversely, in the same patient population, the presence of C-ANCA was associated with a statistically significant increased rate of relapse as compared with P-ANCA (41 vs. 21%, $P = 0.04$) and a decrease in mean time to relapse from 18.5 to 9.3 months (abstract; Hogan, *Clin Exp Immunol* 112:23, 1998). The different associations of disease category or ANCA pattern and the risk of relapse between the nontransplant and transplanted patients could be attributable to the change in the criteria defining each disease category over the years. Consequently, some patients described in the literature as having Wegener's granulomatosis may in fact have microscopic polyangiitis according to the definitions of the Chapel Hill Consensus Conference [29].

The duration of dialysis prior to transplantation had no effect on the rate of relapse. Among the 48 patients for whom this information was available, the median time on dialysis was similar among patients who suffered a relapse and those who did not. This result does not suggest that a delay in transplantation after remission is attained would decrease the risk of relapse post-transplantation.

As in relapsing disease without transplantation, relapses may vary significantly in organ involvement and severity. In our pooled analysis, approximately 60% of patients had recurrent glomerulonephritis either alone

or in addition to other organ involvement, whereas 40% had signs of recurrent extra-renal vasculitis only. The severity of relapse ranged from localized episcleritis only to fatal pulmonary disease [8, 13]. A review of the reports of recurrent ANCA-SVV post-transplantation [12, 15, 16], as well as our pooled analysis, reveals a generally good response to cyclophosphamide in the treatment of relapsing disease as 11 of 16 patients for whom treatment information was available attained either a complete remission or remission on therapy.

The recurrence of vasculitis has also been reported in other autoimmune diseases, although the rates of relapse vary significantly depending on the each disease. For example, the recurrence of Goodpasture's disease after transplantation seems to be exceedingly rare [24]. In systemic lupus erythematosus (SLE), the recurrence of extra-renal vasculitis appears to be about 8%, as reported in relatively large series of patients [30, 31], while the rate of recurrent lupus nephritis seems to be even lower (1.7 to 8.5% of grafts) [30, 31]. The limited information published would therefore suggest that the risk of relapse is higher in ANCA-SVV than in SLE.

There are inherent deficiencies in any analysis that relies primarily on published data. Case reports have been excluded in this analysis because the denominator representing the number of patients with ANCA-SVV undergoing transplantation was not reported. Similarly, small case series tend to overestimate the rate of relapse. Despite these inherent difficulties, the current study benefits from the pooling of 127 patients with ANCA-SVV reported in the literature to date and from our own experience. Only a prospective study of carefully followed patients will circumvent the methodological drawbacks of case series.

In summary, renal transplantation is a beneficial option in the management of patients with ANCA-SVV and end-stage renal disease. Based on these data, the presence of circulating ANCA is not a sufficient contraindication to transplantation. The issue of disease activity is a more difficult one to answer. It is our current practice not to perform transplantation in patients with active vasculitis, but to delay surgery until the disease is in remission. The currently available data do not support the need to wait a certain period of time after remission is attained to perform transplant surgery.

Considering the small number of patients with ANCA-SVV undergoing renal transplantation in any individual center, questions of transplantation in the setting of active disease, the need (if any) to delay of transplantation, and the choice of the optimal antirejection regimen will best be answered by prospectively collecting data in a multicenter registry of patients with ANCA-SVV awaiting transplantation.

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